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## **Long-term experience with oral or inhaled vasodilator combination therapy in patients with pulmonary hypertension**

Beyer, Swantje ; Speich, Rudolf ; Fischler, Manuel ; Maggiorini, Marco ; Ulrich, Silvia

**Abstract:** **BACKGROUND:** Disease progression in pulmonary hypertension (PH) is common despite standard vasodilator monotherapy with iloprost, bosentan or sildenafil. **OBJECTIVE:** To investigate if the combination of these non-invasively applicable treatments is an effective option to address the multiple pathophysiological mechanisms present in PH. **METHODS:** We analysed the clinical course of 23 patients with PH, diagnosed as idiopathic (n = 15), chronic thromboembolic (n = 4), and associated with collagen vascular disease (n = 4), receiving combination vasodilator therapy at our institution. **RESULTS:** Vasodilator therapy before combination therapy consisted of inhaled iloprost (I; n = 12), or oral bosentan (B; n = 6) at a mean duration of 19 +/- 3 months. The combination therapy added was B (n = 8), sildenafil (S; n = 6) or I (n = 4) and in five patients, combination therapy was given from the beginning (3x BS, 1x IS, 1x IBS). Under combination therapy, the 6-minute walk distance (6MWD) increased significantly by 46.7 +/- 24.8 m (p = 0.02) after three months, and after six months it was still 38.3 +/- 28.3 m (p = 0.17) longer than before combination therapy. Respective changes in the Borg Scale and the NYHA functional class were -1.05 +/- 0.49 (p = 0.014) and -0.42 +/- 0.19 (p = 0.02) after three months and -0.21 +/- 0.65 (p = 0.61) and -0.38 +/- 0.29 (p = 0.26) after six months. Only minor side effects were reported. **CONCLUSION:** Combination vasodilator therapy in severe PH is safe and well tolerated. It significantly improves exercise capacity and stabilises the functional class in patients with severe PH deteriorating under single-agent therapy.

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# Long-term experience with oral or inhaled vasodilator combination therapy in patients with pulmonary hypertension

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## Summary

**Background:** Disease progression in pulmonary hypertension (PH) is common despite standard vasodilator monotherapy with iloprost, bosentan or sildenafil.

**Objective:** To investigate if the combination of these non-invasively applicable treatments is an effective option to address the multiple pathophysiological mechanisms present in PH.

**Methods:** We analysed the clinical course of 23 patients with PH, diagnosed as idiopathic ( $n = 15$ ), chronic thromboembolic ( $n = 4$ ), and associated with collagen vascular disease ( $n = 4$ ), receiving combination vasodilator therapy at our institution.

**Results:** Vasodilator therapy before combination therapy consisted of inhaled iloprost (I;  $n = 12$ ), or oral bosentan (B;  $n = 6$ ) at a mean duration of  $19 \pm 3$  months. The combination therapy added was B ( $n = 8$ ), sildenafil (S;  $n = 6$ ) or I ( $n = 4$ ) and in five patients, combination therapy was given

from the beginning ( $3 \times$  BS,  $1 \times$  IS,  $1 \times$  IBS). Under combination therapy, the 6-minute walk distance (6MWD) increased significantly by  $46.7 \pm 24.8$  m ( $p = 0.02$ ) after three months, and after six months it was still  $38.3 \pm 28.3$  m ( $p = 0.17$ ) longer than before combination therapy. Respective changes in the Borg Scale and the NYHA functional class were  $-1.05 \pm 0.49$  ( $p = 0.014$ ) and  $-0.42 \pm 0.19$  ( $p = 0.02$ ) after three months and  $-0.21 \pm 0.65$  ( $p = 0.61$ ) and  $-0.38 \pm 0.29$  ( $p = 0.26$ ) after six months. Only minor side effects were reported.

**Conclusion:** Combination vasodilator therapy in severe PH is safe and well tolerated. It significantly improves exercise capacity and stabilises the functional class in patients with severe PH deteriorating under single-agent therapy.

**Key words:** pulmonary hypertension; vasodilator therapy; combination; bosentan; iloprost; sildenafil

## Introduction

Severe pulmonary hypertension (PH) is a progressive disease with a poor prognosis that ultimately leads to right ventricular failure and death. Although therapeutic options continue to evolve, the treatment of patients with severe PH remains a challenge [1]. Continuous intravenous administration of prostacyclins has been shown to improve haemodynamics, exercise tolerance and survival [2–4]. To obviate the substantial risks, inconveniences and costs associated with continuous intravenous administration, stable prostacyclin analogues for inhaled, oral and subcutaneous application and novel oral substances with different action mechanisms such as endothelin receptor antagonists (bosentan) and phosphodiesterase-5 inhibitors (sildenafil) have been introduced [1, 5–8]. Despite the fact that all these substances have positive effects on PH, they do not provide a cure, so that in many patients the disease progresses despite therapy. The optimal management of patients de-

teriorating under oral or inhaled single therapy is not yet known. Currently, the combination of two non-invasive treatments to circumvent continuous intravenous prostacyclin is being discussed as a potential new therapeutic approach [1, 5, 9]. Therefore, we analysed the long-term performance and outcome of patients with severe PH treated with vasodilator combination therapy at our institution.

### Abbreviations

B	= bosentan
I	= iloprost
PH	= pulmonary hypertension
S	= sildenafil
6MWD	= 6-minute walk distance

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## Methods

### Patient selection

Between July 2002 and October 2004, 23 patients with PH diagnosed as pulmonary arterial hypertension (n = 15 idiopathic, n = 4 associated with collagen vascular disease) and chronic thromboembolic PH (n = 4) receiving vasodilator combination therapy at our institution were included in the study. All patients provided written informed consent. Patients' characteristics before combination therapy are shown in table 1. Patients were considered for combination vasodilator therapy when they either deteriorated under vasodilator monotherapy or were too ill for monotherapy at baseline, and, therefore, were considered to need non-invasive vasodilator combination therapy. Patients under monotherapy were included when at least two of the following criteria were fulfilled: 1) subjective impairment, 2) deterioration in 6-min walk distance of more than 20%, 3) clinical signs of right heart failure despite optimisation of diuretic therapy, 4) recurrent syncope. Patients, in whom vasodilator combination therapy was started immediately from the beginning, fulfilled at least one of the following criteria: 1) 6MWD below 150 m, 2) NYHA functional class IV, 3) cardiac index less than 2 l/min/m<sup>2</sup>, 4) mixed venous oxygen saturation below 50% and non-willingness to undergo or contraindication to continuous intravenous iloprost therapy.

### Vasodilator treatment

The treatment consisted of inhaled iloprost (I), oral bosentan (B), oral sildenafil (S) and their combinations [1]. For inhalation of iloprost (Ilomedin®, Schering AG, Berlin, Germany) the recommended special inhalation device Optineb® (Nebu-Tec AG, Elsenfelden, Germany) was used to obtain iloprost particles at a mean diameter of 3 µm, which are known to reach the alveoli and remain there for some time without being exhaled immediately. Inhaled iloprost was started at a daily total dose of 25 µg and slowly increased to the target daily dose of 100 µg divided into five to six single inhalations of about five minutes. Oral bosentan (Tracleer®, Actelion AG, Baden, Switzerland) was started at a dose of 62.5 mg bid and increased to the target dose of 125 mg bid after one month; initially, the liver enzymes were monitored fortnightly, then monthly as recommended. Sildenafil (Viagra®, Pfizer, Zurich, Switzerland) was started at a dose of 12.5 mg tid and increased fortnightly to the target dose of 50 mg tid.

### Follow-up and prospective assessments

All patients were closely followed up for therapeutic effect, tolerance, side effects and signs of clinical deterio-

ration at our institution. The NYHA functional class was assessed using the modified WHO-criteria [10], the 6MWD test was performed as recommended [11] and supplemented with the Borg's rating of perceived exertion scale obtained at the end of the 6MWD test. Hereby, a scale from 1–10 was used, with one signifying none and ten maximal perceived exhaustion [12]. All measures were assessed prospectively at baseline, at three and at six months of combination therapy.

### Retrospective assessments

The records of study patients already under monotherapy were reviewed for the duration of monotherapy, 6MWD, Borg Scale and NYHA functional class at the beginning of vasodilator therapy and three and six months thereafter. Additionally, the patient records were reviewed for self-assessed quality of life using the Minnesota Living with Heart Failure Questionnaire (MLHF-q) [10, 13, 14], a 21-item instrument previously validated for PH patients at our clinic [15]. With the MLHF-q patients assess how much the disease impacts their physical, socio-economic and psychological aspects of daily life from 0 (not at all) to 5 (very much). Scores on the total instrument range from 0 to 105, with higher scores representing lower quality of life. The first eight questions relate primarily to physical functioning (physical subscore), whereas the last five are more about emotional aspects (emotional subscore); the remaining questions relate to general aspects.

### Patients' survival

We compared survival of the present cohort, treated with a strategy to switch to vasodilator combination therapy in case of clinical worsening or to start immediate combination therapy in case of high-risk baseline values, with a historical cohort of PH patients included in the American National Institute of Health Registry [16].

### Statistics

All baseline data and graphic illustrations are given as the mean and standard error of mean (s.e.). The Wilcoxon Signed Rank Test was used to assess significant differences (with two-sided p value) in the 6MWD, Borg Scale and NYHA functional class. The standard life table method was used for analysis of survival (SPSS version 12.0, Software GmbH, Munich, Germany). A p < 0.05 was considered significant.

## Results

### Study population and baseline characteristics

The characteristics of the present patient population are shown in table 1. The mean duration of previous vasodilator monotherapy with inhaled iloprost (12 patients) or oral bosentan (6 patients) was 19 (3) months. The combination therapy added was B (n = 8), S (n = 6), and I (n = 4). Patients starting primarily with combination therapy were given B and S (n = 3), I and B (n = 1), and all three I, B, and S (n = 1).

### Retrospective analysis of performance during vasodilator monotherapy

During vasodilator monotherapy, the 6MWD decreased by 35 (28) m (from 368 (31) to 334 (33), p = 0.22) after an initial increase during the first 6 months (figure 1), the Borg Scale significantly increased by 1.7 (0.6) (p = 0.03), and the NYHA functional class significantly increased by 0.72 (0.21) (p = 0.007) (figure 2). From nine patients under initial monotherapy complete MLHF-q were available at baseline and before combination therapy, the mean total score, physical subscore

and emotional subscore increased by 10.3, 3.1 and 2 points, respectively. Haemodynamic data obtained by right heart catheterisation could be retrieved from 12 out of the 18 patients, the mean values during vasodilator monotherapy changed as follows: mean pulmonary artery pressure +4.9 mm Hg, pulmonary vascular resistance +147  $\text{dyn}\cdot\text{s}\cdot\text{m}^{-5}$ , cardiac index  $-0.1 \text{ ml/min/m}^{-2}$ , mixed venous oxygen saturation  $-2.1\%$ . The right ventricular above right atrial pressure calculated from the tricuspidal regurgitation jet assessed by transthoracic echocardiography increased by 4.1 mm Hg.

#### Analysis of performance during the six months prospective observational period under vasodilator combination therapy

During vasodilator combination therapy, the overall 6MWD significantly increased by 47 (25) m ( $p = 0.02$ ) after three months, and after six months, it was still 38 (28) m ( $p = 0.17$ ) higher than before combination therapy (see figure 1 for performance of individual patients). Respective changes in the Borg ratings and NYHA functional class were  $-1.0$  (0.5) ( $p = 0.014$ ) and  $-0.4$  (0.2) ( $p = 0.02$ ) at three months and  $-0.21$  (0.65) ( $p = 0.61$ ) and  $-0.38$  (0.29) ( $p = 0.26$ ) at six months. Nine patients, all belonging to the group which was initially treated with monotherapy, returned MLHF-q after the observational period with vasodilator combination therapy, the mean total score, physical subscore and emotional subscore declined by 7.6, 2.5 and 3.8 points, respectively. Hereby, the decline in the emotional subscore reached statistical significance ( $p = 0.048$ ).

#### Additional follow up and comparison of survival

Mean predicted survival for the present study cohort according to the NIH formula (National Institute of Health) [16] is calculated at 71% after one, at 59% after two and at 51% after three years. We followed up 22, 18 and 13 of the 23 patients of the present cohort for one, two and three years, respectively. From the 22 patients followed up during the first year, one patient died 8 months after start of combination therapy due to disease progression (scleroderma), all other patients survived (percentage of survivals of our cohort and the NIH-cohort is shown in figure 4). Pulmonary haemodynamics assessed 10 (4) months after onset of combination therapy by right heart catheterisation (7 patients) and echocardiography (12 patients) showed the following respective changes: mean pulmonary artery pressure  $-12 \text{ mm Hg}$ , pulmonary vascular resistance  $-326 \text{ dyn}\cdot\text{s}\cdot\text{m}^{-5}$ , cardiac index  $+0.6 \text{ ml/min/m}^{-2}$ , mixed venous oxygen saturation  $-5.5\%$  and echocardiographical right ventricular/right atrial pressure  $-12 \text{ mm Hg}$ .

#### Adverse events

The combination therapy was well tolerated by all patients, none of them stopped the combination therapy, and none of the patients died during the six-months study period. Reported side effects were comparable between therapies. They were only minor and consisted of dizziness (5 patients, 3 ib, 1 is, 1 ibs), flush (3 patients, 2 bs, 1 ib) and headache (5 patients, 2 ib, 2 is, 1 bs), agitation and sleeplessness (1 patient, ib) and minimal peripheral oedema (3 patients, 2ib, 1 is), and the therapy was not changed because of side effects. One patient received lung transplantation at seven month of combination therapy and was not evaluated thereafter.

## Discussion

**Table 1**

Patients' characteristics and haemodynamics before onset of combination therapy.

Age	50 (3)
Sex females/males	14/9
NYHA functional class II/III/IV	1/4/18
Body mass index	25 (1.2)
6-minute walk distance (m)	330 (33)
Borg dyspnoea scale	6 (0.5)
Mean pulmonary arterial pressure (mm Hg)	50 (4)
Pulmonary vascular resistance ( $\text{dynes}\cdot\text{s}\cdot\text{cm}^{-5}$ )	868 (112)
Cardiac index ( $\text{l}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ )	2.4 (0.2)
Mixed venous oxygen saturation (%)	62 (3)
Right ventricular/atrial pressure in echocardiography	70 (26)
Initial therapy bosentan/inhaled iloprost/none	6/12/5
Time on monotherapy until combination therapy (months)	19 (3)

NYHA: New York Heart Association; data are given as mean and standard error of mean ()

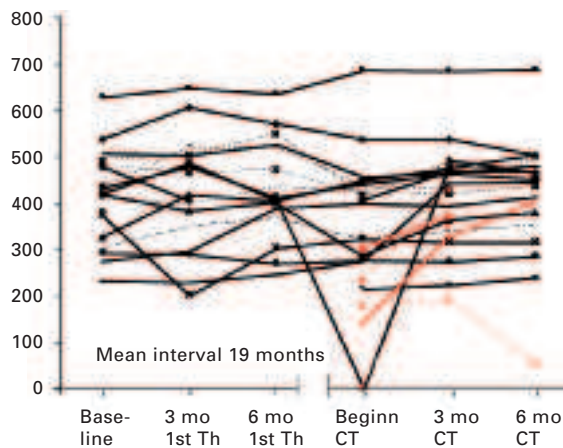
This prospective observational study indicates that combination of oral or inhaled vasodilator therapy improves dyspnoea, exercise capacity and Borg scale in severely ill patients with advanced PH. In addition, survival of these patients might be improved.

All patients in the present series had advanced PH before onset of combination therapy confirmed by pulmonary haemodynamics, clinical assessments and 6MWD (table 1). Patients treated with second-line combination therapy had previously received standard, non-invasive vasodilator first-line therapy with oral bosentan or inhaled iloprost [6, 17] as recommended. Sildenafil was not used as first-line therapy in this study, as results of its beneficial effect on PH were published after study initiation [7, 8]. Although in most patients, the first-line therapy resulted in clinical improve-

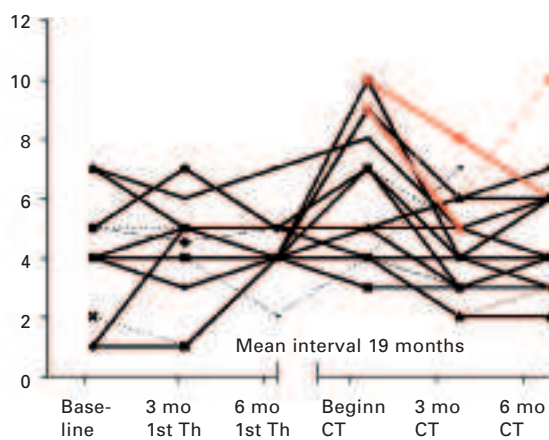


**Figure 1**

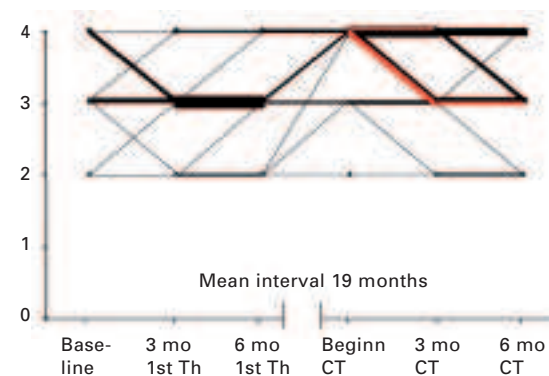
Change in six-minute walk distance. CT = combination therapy, mo = months, th = therapy. Every line shows the course of a single patient. Black lines are used for patients with initial monotherapy, red lines for patients with CT from the beginning. Patients with IPAH are represented by plain lines, patients CTEPH by dotted lines and patients with PH associated with collagen vascular disease by dashed lines.

**Figure 2**

Change in Borg Scale ratings. CT = combination therapy, mo = months, th = therapy. Every line shows the course of a single patient. Black lines are used for patients with initial monotherapy, red lines for patients with CT from the beginning. Patients with IPAH are represented by plain lines, patients CTEPH by dotted lines and patients with PH associated with collagen vascular disease by dashed lines.

**Figure 3**

Course of NYHA class under first mono- and combination therapy. CT = combination therapy, mo = months, th = therapy. Lines show course of patients NYHA class over time. Thickness of line represents number of patients (0.5 pts/per patient). Patients with initial CT are depicted in red.



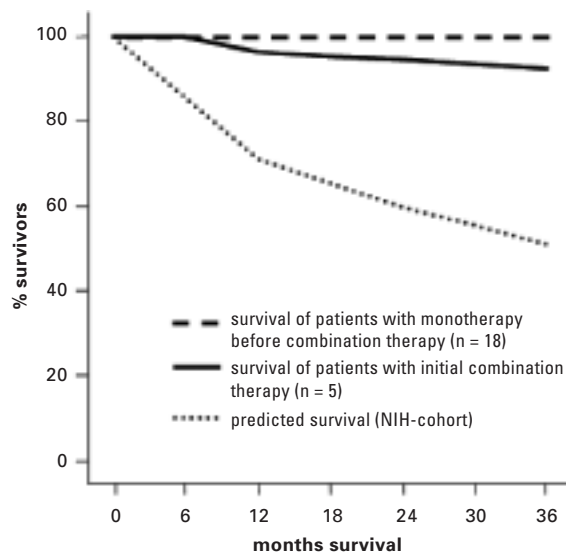
ment and increase in exercise tolerance (figure 1–3), this effect did not last. After an average period of one and a half year these relatively young patients showed clinical deterioration with a marked decline in 6MWD (figure 1), higher ratings of perceived exertion on the Borg Scale and higher NYHA class (figure 2 and 3). The unfortunate clinical reality is that even with novel target treatments available for PH, a number of patients deteriorates after initial improvement. Those patients usually have a dismal prognosis and will eventually die from their underlying disease with-

out aggressive therapy [1, 5, 16]. Until recently, the only valuable therapeutic alternative for this group of patients was continuous intravenous prostacyclin therapy [2, 4] or lung transplantation. However, continuous intravenous prostacyclin therapy is inconvenient for the patients, and it bears a considerable risk of catheter-related diseases (infections, thrombosis) and of rebound PH following accidental discontinuation. The most recent World Symposium on PH therefore postulated that combination of preferably non-invasive vasodilator treatment might be an alternative to continuous intravenous therapy [1]. Although only a few non-randomised observational studies about vasodilator combination therapy in PH have been published to date, the available data are promising [9, 18–21]. In line with this, we found a significant improvement of performance after three months in our collective. The sustained response after six months together with the comparatively beneficial survival and preliminary haemodynamic follow-up data are encouraging. However, a temporarily vanishing or even non-response might nonetheless be expected for some patients. Our cohort study emphasises the effect of vasodilator combination therapy on the care of severely ill PH patients, especially on those deteriorating under monotherapy. Moreover, vasodilator combination therapy seems to be a highly effective first-line therapy for patients in NYHA class IV, as seen in the five patients of the present cohort, who were given combination therapy from the beginning. In four of the five patients, combination therapy was started at the intensive care unit. All of them improved considerably and left the hospital walking. Combination therapy was well tolerated by all patients and proved to be efficient in this “negatively” selected subgroup of patients with very severe and progressive disease. In addition to the significant improvement in exercise capacity, exhaustion and dyspnoea functional class (figure 1–3) we also found an improvement in the self-assessed quality of life score in the patients who returned the MLHF-q. However, due to the small patient number, only the improvement of the emotional subscore was statistically significant.

Our strategy of combining vasodilator therapy in patients either presenting with advanced disease with dismal prognosis at baseline or patients who deteriorate under monotherapy seems to be justified also by the considerable improvement in survival in our study population compared with the predicted survival in the NIH-cohort (figure 4) [16]. However, these results have to be interpreted with caution because the present series is quite small and there have been 14 years of medical advancement since the results from the NIH-cohort study by Alonzo et al. were published. Nonetheless, we believe, with respect to the pronounced differences in the predicted and the observed survival curves, that the strategy including vasodilator combination therapy might be highly effective in patients with advanced PH.

**Figure 4**

Survival of present cohort compared with predicted survival (NIH-cohort, Alonzo et al. [16]).



Obviously, this observational study has several inherent limitations: there was no control group, the patient population was small and the overall observation time was rather short. In addition, treatment with bosentan, inhaled iloprost and sildenafil was not part of a formal study protocol, and the patients had only one right heart catheter examination, so that haemodynamic follow-up data were not available. Although invasive data might be of value, it is accepted good clinical practice to make

therapeutic decisions mainly relying on the patients' functional classification, the 6MWD and the overall clinical judgment [1, 18, 22, 23].

Our study population consisted of high-risk patients, who were rapidly deteriorating under standard vasodilator therapy and needed immediate access to new therapies. This high-risk cohort showed a favourable clinical response to oral or inhaled vasodilator combination therapy. Further adequately powered randomised controlled trials on the efficacy of non-invasive combination therapy are warranted, our preliminary data show that under close monitoring by an experienced team, non-invasively applicable combination therapy is an effective and save therapeutic option for severely ill PH patients.

In summary, our data provide preliminary but highly encouraging evidence that combination vasodilator therapy in severe PH is safe, effective and convenient.

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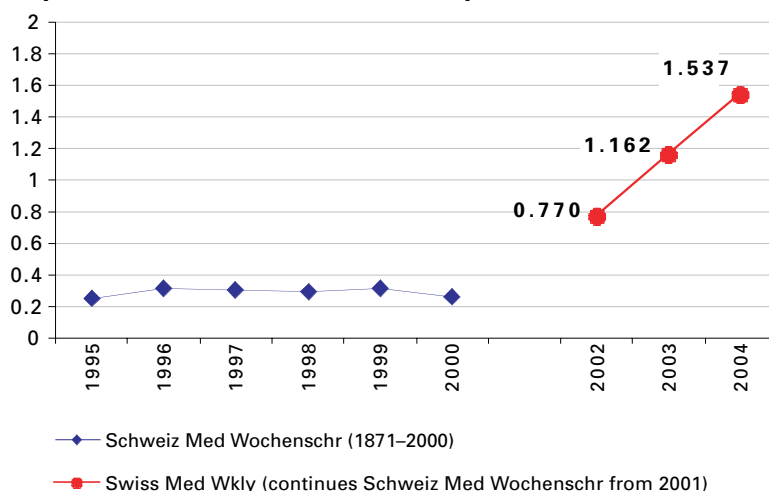
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